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Review

Regulation of cell volume and water transport – An old fundamental role of the renin angiotensin aldosterone system components at the cellular level

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ABSTRACT

The expression and the role of renin angiotensin aldosterone system (RAAS) components on regulation of cell volume and water transport on vertebrates and invertebrates were reviewed. The presence of these components even in simple organisms like leeches and their relevance for the control of cellular volume and water transport supports the view that the expression of these components, at cellular level, is an acquisition which was preserved throughout evolution.

Contents

Introduction

The preservation of cell volume is fundamental for cell survival requiring the presence of regulatory mechanisms such as the regulatory volume decrease (RVD) or the regulatory volume increase (RVI). The inhibition of RVD has serious consequences for cellular function leading to activation of membrane ionic channels and of several kinases resulting in abnormalities of cellular function and is commonly associated with cell shrinkage through activation of AKt1 [21]. Furthermore, changes in cell volume can represent signals triggering cell migration, proliferation and release of hormones and transmitters [21]. Cell swelling occurs during hypothermia and hypoxia/ischemia, increase in the extracellular K+ concentration [K+] as well as intracellular acidosis/diabetic ketoacidosis. Variations in cell volume are not necessarily associated with extracellular hypotonicity or hypertonicity because increase of intracellular osmolarity due to synthesis or elimination of osmolytes, is responsible for cell swelling [21].

Evidence is available that in mammals, there are local renin angiotensin systems in different organs including the heart, kidney and possibly in the brain in which RAAS components have been identified intracellularly (see 7,11,13,10,40). These findings might indicate that the intracrine RAAS characterized by intracellular synthesis of RAAS components or their internalization, plays an important role on cellular functions. Here we review the question whether the expression and function of RAAS components on cell

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volume and water transport is an old event preserved throughout evolution.

RAAS components are present in cells of invertebrates

Evidence is available, for instance, that components of the RAAS are present in invertebrates including annelids [38], crustaceans [5,6], molluscs [17], insects [20,32,34,35]. In leech (*Theromyzon tessulatum*), brain neurons immunoreaction to angiotensin II has been described [30] and immunocytes showed immunoreactivity to antihuman-Ang II and antihuman AT1 receptors [29,30]. Also, an asparyl protease of 32 kDa exhibiting 35% of sequence identity with mammalian renin, has been found in the leech [28,30]. Biochemically, renin, ACE- and AT1-like receptor were identified in the leech immune cells [28] and ACE has been found in bacteria [26]. So far, only soluble, single domain ACEs from invertebrates have been cloned, and these have been implicated in reproduction in insects [18]. Interestingly, bacterial DNA sequences could encode putative ACE-like proteins, strikingly similar to vertebrates enzymes [26]. ACEs from invertebrates have been isolated from insects like *Drosophila melanogaster* [5] showing kinetics very similar to mammalian ACE [26]. Immunochemical studies indicated ACE intracellularly co-localized with myotropine peptides suggesting a convertase activity [18]. Immunostaining of leech sections, revealed labeling in neurons and glial cells of the central nervous system (CNS), immunocytes, the nephridial canal canaliculi and the periphery of the ciliated funnel, as well as the epithelium lining nephridia. Renin is localized in the excretory system and in the nervous system of leech [29,30] and its first appearance has been detected in bony fish [16]. The first genomic characterization of non-mammalian vertebrates renin genes found in zebrafish was recently described [22]. According to Fournier et al. [16], practically all components of the renin angiotensin aldosterone system appear in bony fish with exception of Mas receptor of Ang (1–7) which appeared in amphibians.

On the functions of RAAS components in invertebrates

An important question is the physiological meaning of the expression of RAAS components. For many invertebrates, an important factor for survival when the medium changes, is the capability of the sodium pump to regulate the increased intracellular sodium concentration caused by an incremented osmolarity of the medium [25]. Evidence is, available that Ang II regulates water flow through aquaporins in clam worm [31] and experiments performed on leeches in vivo, indicated that Ang II amide is involved on the control of water balance [28]. Measurements of transepithelial short-circuit current in leeches, showed that Ang II amide reduced this current-an effect mediated by Cl− secretion [25,31] and in consequence, water follows the peptide eliciting water loss across the epithelium.

Cell swelling is known to activate ionic channels like the swelling-dependent chloride channel ($I_{Clswell}$) which plays an important role on the regulation of cell volume [3,7–9,19]. Eggs of the ascidian *Boltenia villosa* have an inwardly rectifying Cl− current whose amplitude varies by more than 10-fold during each cell cycle and osmotically produced swelling also increased Cl− current amplitude in unfertilized eggs [38]. These findings indicate that RAAS components play an important role on regulation of cell volume and water transport.

Components of RAAS are involved in cell volume regulation in vertebrates

The appearance of a sophisticated kidney function in mammals made it possible the efficient regulation of blood volume and blood pressure through the activation of the systemic renin angiotensin aldosterone system (RAAS). Independently of a circulatory RAAS, the expression of RAAS components at cellular level in vertebrates because immunodetection of renin–angiotensin system (RAS) components were found in anterior pituitary cells, particularly in lactotropes [36] and prorenin, renin and angiotensinogen were identified not only in lactotropes and gonadotropes but also in somatotropes, corticotropes, and thyrotropes. The highest levels of renin were detected in lactotropes and gonadotropes [37]. The detection of angiotensinogen and both its specific cleavage enzyme and its proenzyme within the same granule, suggests intragranular processing of this component [37] indicating an important intracrine mechanism involved in the secretory process.

In mammalians, components of the renin angiotensin system have been detected in several tissues including the heart, adrenal gland, kidney and in the brain [9,12,19,27,37,40] and many of the old properties of RAAS components as regulators of cell volume and water transport seen in invertebrates, are present in the mammalians. The RAAS is involved in the regulation of cell volume in normal mammalian heart as well as in the failing heart [7]. Indeed, in myocytes isolated from the failing ventricle and exposed to renin plus angiotensinogen or to Ang II, an increase of cell volume was seen concurrently with the inhibition of the sodium pump [7] while the intracellular administration of Ang II had an opposite effect [9]. The activation of the Na–K–2Cl cotransporter is involved in the effect of Ang II because bumetanide abolished the swelling induced by the peptide [9]. The regulation of cell volume, involves other components like ion channels and their voltage dependence. Cell swelling induced by Ang II in cardiac cells, causes the activation of ionic channels like the swelling-activate chloride current ($I_{Cl,swell}$) [3] leading to membrane depolarization, reduction of action potential duration [7] and consequent changes in cardiac excitability. The increase of ($I_{Clswell}$) in the failing and in the normal mammalian heart [3,8] elicited by changes in cell metabolism or by Ang II, is particularly relevant because the activation of this current seems involved in generation of cardiac arrhythmias including early after depolarizations [8].

In mammals, cell swelling also activates potassium channels (K(v) 4.2/4.3) which are the primary subunits of $I_{(to,fast)}$, through phosphorylation/dephosphorylation of serine/threonine phosphatases [39] in the mammalian heart [7,39]. It is known, for instance, that Ang II causes cell swelling and increases ICl_{swell} in the failing as well as in normal heart [3,8] and that the inability of the heart cell to regulate its volume through a lack of activation of the regulatory volume decrease (RVD) leads to serious impairment of heart cell function [21]. Components of the renin angiotensin system in the myocardium [19] play an important role on regulation of cell volume and water transport because extracellular Ang II or renin inhibit the sodium pump, counteracts the decline in cell volume. On the other hand, when the cell is exposed to hypotonic medium, the increment of cell volume can be reduced by intracellular Ang II or renin [7]. In this way, RAAS components contribute to the regulation of cell volume. This physiological property of Ang II is quite old because evidence is available that the peptide suppressed body weight loss of the clam worm *Perinereis* sp. under a hyper-osmotic condition, and enhanced body weight gain under a hypo-osmotic condition [31].

On the role of aldosterone and mineralocorticoid receptor

The earliest corticoid receptor have been found in lamprey and hagfish. The mineralocorticoid (MR) and the glucocorticoid (GR) first appear in skates and sharks while aldosterone first appears in lobe-finned fishes [1,24,33]. A mutation corresponding to His-950 in human MR may have been important in the physiological

changes associated with emergence of Old World monkeys from prosimians [2,4]. Bridgham et al. [4] provide strong evidence that a GR with a preference for cortisol over aldosterone, arose in an elasmobranch descendent that was the common ancestor of ray finned fish and land vertebrates.

It is well known that aldosterone is a steroid hormone involved in the regulation of blood volume, salt and water homeostasis. Although aldosterone has a genomic effect by activating the mineralocorticoid receptor, a rapid action of aldosterone has been described. The mechanism involved in this rapid effect of the hormone, probably involves interaction with Ang II.

Evidence is available that the mineralocorticoid receptor is involved in the regulation of cell volume. The increase in cell volume caused by extracellular Ang II in cardiac cells of the mammalian heart, for instance, was enhanced when the cells were incubated with aldosterone for 48 h [13] – an effect abolished by spironolactone. The mineralocorticoid receptor is an important component of the intracrine action of Ang II because the decline in cell volume elicited by intracellular administration of Ang II, was increased by aldosterone and inhibited by spironolactone [13]. The effects of aldosterone and spironolactone were related, in part, to a change in expression of AT1 receptors at surface cell membrane [13].

ACE2, angiotensin (1–7) and cell volume

ACE2 [14] belongs to the angiotensin-converting enzyme family of dipeptidyl carboxydipeptidases and has considerable homology to human angiotensin 1 converting enzyme [14]. In addition to regulation of cardiovascular and kidney function, the encoded protein is a functional receptor for the spike glycoprotein of the human coronaviruses SARS. Angiotensin II is hydrolyzed to angiotensin (1–7) by ACE2 [14] with consequent generation of angiotensin (1–7), which counteracts some harmful effects of Ang II [15] including the block of impulse propagation seen during ischemia/reperfusion [11]. According to Fournier et al. [16] the first appearance of Ang (1–7) Mas receptor was in amphibians suggesting that ACE2 also appears in amphibians.

Mutation of angiotensin-converting enzyme-related (ACER) gene, a Drosophila ACE2 homolog, was proven to result in a severe defect during heart morphogenesis and regulates heart physiology in adult flies [23]. ACER also plays an important role in regulating sleeping behavior [23].

Ang (1–7) generated from angiotensin II [14] in vertebrate animal models and humans [14,41], has been found to counteract many effects of Ang II [14], reduces the heart cell volume and the swelling-activate chloride current ($I_{Cl,swell}$) enhanced by Ang II [9]. Since cell swelling induced by myocardial ischemia or heart failure, represents an important arrhythmogenic mechanism, the formation of Ang (1–7) through the activation of the ACE2/Ang (1–7)/Mas receptor axis might be of benefit to the ischemic heart [9]. The beneficial effect of angiotensin (1–7) on impulse propagation seen under these conditions, is related to the activation of the sodium pump and hyperpolarization of cell membrane [11]. ACE2 is over-expressed during heart failure leading to a higher formation of Ang (1–7) [41] and recent findings indicate that angiotensin (1–7) increments the sodium pump and reduces the cell volume by 15% within 25 min in the failing heart [7,9]. It is then conceivable, that the improvement of cardiac function and decreased incidence of cardiac arrhythmias during ischemia/reperfusion elicited by Ang (1–7), be related, at least in part, to the decrease of heart cell volume. According to these observations, the balance between ACE and ACE2 expression seems to be a determinant factor on the regulation of heart cell function and volume. Although evidence is available that the Mas receptor for Ang (1–7) first appear in amphibians [16], no information is available on the role of the hexapeptide on cell volume and water transport on invertebrates.

Perspectives

(1) The presence of RAAS components in cells of invertebrates and their role on the regulation of cell volume and water transport, represents an important acquisition which was maintained throughout evolution; (2) the organization of a renin angiotensin aldosterone system only appeared later on the evolutionary scale; and (3) although the intracellular and extracellular expressions and functions of ACE, ACE2, angiotensinogen, renin and Ang II preceded the appearance of a sophisticated circulating renin angiotensin system, its acquisition represents an important regulatory factor of cellular homeostasis in mammals.

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